Risk factors and long-term treatment in obstructive airways disease.

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Chapter 14

Summary and discussion

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14.1 Summary

The multi-centre study which is described in this thesis was performed in patients with obstructive airways disease, including both asthma and chronic obstructive pulmonary disease (COPD). Asthma is a syndrome characterized by attacks of dyspnea or wheezing and variable airways obstruction. The clinical hallmark is increased airways responsiveness which in part reflects the underlying chronic inflammatory process. COPD is a chronic disease with fixed airways obstruction and is closely related to smoke inhalation. It is characterized by a progressive loss of lung function. Epidemiological data point to a worldwide rise in mortality from COPD. Such a rise, however, occurs in asthma as well, but not invariably in all countries, especially not in the Netherlands for some ill-understood reason. Morbidity associated with asthma and COPD is considerable: approximately 10-20% of the Dutch population has the characteristic respiratory symptoms.

Intermittent or not, both asthma and COPD cause chronic symptoms and lung function abnormalities which in many cases elicit the use of medication, often for years on end. Surprisingly, the majority of clinical trials to date have assessed only the short-term efficacy of various drugs for obstructive airways disease.

In view of the ongoing high morbidity and mortality of obstructive airways disease, it is important to firstly determine risk factors for the development and further progression of the disorder, and secondly to try to influence these risk factors with either preventive measures or treatment in order to improve the course and prognosis of the disease. For asthma, prognosis is primarily related to the levels of airways obstruction and hyperresponsiveness. In COPD, prognosis is primarily related to age and initial level of airways obstruction, and next to smoking, airways hyperresponsiveness, and perhaps to reversibility of obstruction. Hence, asthma and COPD share the presence of obstruction and hyperresponsiveness as risk factors in disease prognosis.

In the present study two central hypotheses were tested:

1. Treatment aimed at redressment of both common risk factors for progression of disease, i.e. airways hyperresponsiveness (by an inhaled corticosteroid) and airways obstruction (by a β_2-agonist) compares favourably in long-term prognosis to symptomatic treatment of airways obstruction alone (by a β_2-agonist).
2. More vigorous bronchodilation with both an inhaled β_2-agonist and an anticholinergic offers long-term benefits in disease prognosis as compared to a β_2-agonist alone.

The general methods of the study are described in **chapter 2**. It was designed as a multi-centre randomized clinical trial with a follow-up of 3 years. Patients were randomly assigned to one of three parallel treatment arms. From identical, blinded metered dose inhalers, all patients received a β_2-agonist (terbutaline sulphate two puffs of 250μg four times daily) with additionally in a second canister either:
1) a corticosteroid (beclomethasone dipropionate two puffs of 100μg four times daily)
2) an anticholinergic (ipratropium bromide two puffs of 20 μg four times daily)
3) a placebo (also two puffs four times daily).

Much effort was put into the standardization of lung function measurements and the bronchial provocation tests. A three months feasibility study was found to be extremely useful in eliminating minor problems from the study protocol.
Since the following factors are all characteristics of the disease at any given moment and can therefore be considered possible confounders of a treatment effect, the randomization was carefully stratified for these factors and their influence on treatment effects was subsequently analyzed. The disease characteristics stratified for were: airways obstruction, airways hyperresponsiveness, reversibility of airways obstruction, age, gender, smoking habit, atopy, and prior use of inhaled corticosteroids. Stratification was done by minimization method and resulted in well-balanced treatment groups for all above factors and participating centre. It was performed on a personal computer by an independent central 24 hour service telephone centre.
The 274 patients enroled into the study were divided into symptom-based diagnosis groups using data from a standardized history, adhering as best we could to the criteria of the American Thoracic Society. Patients reporting attacks of breathlessness and wheeze (asthmatic attacks) without chronic (i.e. for more than 3 months per year) cough or sputum production were identified as having asthma (37%). Current or former smokers without a history of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnea when walking quietly on level ground, or both, were included in the COPD group (20%). Patients with both asthmatic attacks or recurrent wheeze and chronic cough and sputum production were labelled asthmatic bronchitics (31%). Subjects with insufficient data to establish a diagnosis from history taking were included in an undefined diagnosis group (12%).

Atopy is an important parameter in the diagnostic work-up of patients with asthma and COPD. Atopic status is routinely assessed by history taking and measurement of objective parameters of atopy. The relative merits of these different parameters is only partially known. In **chapter 3**, the relationships between allergic symptoms, allergy parameters (skin test to house dust mite, total IgE, house dust mite specific IgE, and blood eosinophil counts), and several confounding variables were assessed. Skin tests to house dust mite proved to be better predictors for allergic symptoms than total or specific IgE levels and eosinophil counts. The other allergy parameters gave no additional information on symptoms once the skin test was known. Expressing the skin test relative to the positive control was slightly better than the uncorrected wheal size and cut-off values for a positive skin test are presented which are useful in both asthma and COPD.

The main results of the intervention trial are presented in **chapter 4**. The study was terminated after 2.5 years instead of the 3 years that were originally planned, because of predefined, large differences in drop-out rates and primary endpoints in favour of patients treated with inhaled corticosteroids. The most striking result was the large difference in withdrawal rates: almost 50% of patients who did not receive inhaled corticosteroids withdrew from the study as compared to only 13% of those who did receive steroids. Sixty four percent of withdrawals were caused by deterioration of clinical status in patients on bronchodilators only. In line with this, exacerbations rates were approximately 0.75 per patient-year in both bronchodilator groups compared with 0.25 in the corticosteroid group. Airways obstruction, as measured by FEV_1, improved by 10%predicted in patients receiving steroids as compared to those who did not. This difference was obtained within 3 months of therapy, to remain approximately stable afterwards. Airways hyperresponsiveness, as measured by PC_{20}, improved by 2.0 doubling doses in the group with steroids compared to no change in the other two groups. The largest part of this improvement occurred during the first 6 months of treatment, but afterwards airways hyperresponsiveness continued to decrease further. Non-smokers, allergic patients, and patients younger than forty years benefitted more from the addition of inhaled corticosteroids than smoking, non-allergic, and older patients, but in all subgroups improvement occurred compared to the same subgroups not receiving inhaled corticosteroids. No significant long-term differences were found between patients receiving only a $ß_2$-agonist and those additionally receiving an anticholinergic, even though acute bronchodilation was greater with ipratropium bromide plus terbutaline than with terbutaline alone.

Airways hyperresponsiveness is the hallmark of asthma and it can also be demonstrated in many patients with COPD. It has been suggested, however, that in patients with COPD, airways hyperresponsiveness is closely related to the baseline FEV_1, thus implying that the increased responsiveness in COPD largely is an artifact. By contrast, airways hyperresponsiveness in asthma is supposed to be largely determined by the inflammatory process in the airway wall, and not by airway diameter. These differences are challenged in **chapter 5**. For each level of prechallenge FEV_1, patients with asthma showed a lower PC_{20} value than patients with COPD. The dependence of PC_{20} on prechallenge FEV_1, however, was comparable in all diagnosis groups. That a real airways hyperresponsiveness can be found in patients with COPD is compatible with clinical symptoms of increased breathlessness with cold air or fog found in many patients with COPD.
The relationship of airways hyperresponsiveness to respiratory symptoms and peak flow variation were found to be low cross-sectionally, suggesting that all these parameters may provide different information on the actual disease state. No significant differences were found between symptom based diagnosis groups with respect to diurnal peak flow variation.

The effect of long-term treatment on the relationship between symptoms, airways hyperresponsiveness, and diurnal peak flow variation was assessed longitudinally in **chapter 6**. Morning peak flows increased markedly, as did afternoon peak flow to a lesser extent. As a consequence, peak flow variability diminished with steroids. The

within-subject, or longitudinal relationship of changes in peak flow variation with PC_{20} was found to be relatively weak; the relationships with changes in symptom scores, FEV_1, and bronchodilator response were even weaker. The results presented in this chapter lend support to several international guidelines on asthma management that the peak flow meter is a feasible and valuable instrument to follow lung function level at a daily basis at home, but questions the measurement of peak flow variation as a proxy of airways hyperresponsiveness.

Results of bronchodilator response tests are commonly used as a basis for disease classification and choice of treatment by clinicians, and as an inclusion criterion for studies by research workers. Despite these important functions of bronchodilator response testing, there is no agreement on how to express the results. Four different expressions of the bronchodilator response were compared cross-sectionally in **chapter 7**. Expressing the response relative to the baseline or initial value is the most commonly used method, but it is demonstrated that this expression has the undesirable property of being much more dependent on initial FEV_1 than for instance expressing the response relative to the predicted FEV_1. This latter expression had the highest likelihood of separating patients with a symptom-based diagnosis of asthma from those with COPD. Despite significant differences in mean response, large overlap of individual responses, in whatever way expressed, occurred between diagnostic subgroups.

In **chapter 8**, the same four expressions of bronchodilator test results as in chapter 7 were examined longitudinally for 2.5 years. Changes during steroid and bronchodilator therapy were evaluated, as well as long-term variability, and prognostic value of the bronchodilator response in predicting response to inhaled corticosteroids. Bronchodilator responses decreased substantially with inhaled corticosteroid therapy; this decrease could only partially be explained by an increase in prebronchodilator lung function. Bronchodilator responses were highly variable: as a result less than half of the patients could consistently be classified as "reversible" or "irreversible". These data indicate that decisions to label a patient's obstruction as "irreversible" should not be based on a single bronchodilator test and should be made with taking the effects of anti-inflammatory therapy into account. The bronchodilator response at the start of the study proved to be a poor predictor of corticosteroid induced improvement in FEV_1 in the first three months of treatment, when the changes in FEV_1 are most prominent.

Many patients with obstructive airways disease show improvement in FEV_1 and PC_{20} during inhaled corticosteroid therapy, but the extent of the improvement varies considerably between patients and studies. As it is unknown which patient characteristics determine the differing response, we analyzed the independent influence of several patient characteristics on improvement in FEV_1 and PC_{20} during inhaled corticosteroids in **chapters 9 and 10**, respectively. The more hyperresponsive patients, and independently of that, the more allergic patients, and non-smoking patients showed a larger improvement in FEV_1 during the first three months of inhaled corticosteroid therapy than less hyperreactive, less allergic and smoking patients. Total IgE proved a better independent predictor of this short-term response to corticosteroids than specific IgE for house dust mite, skin tests, or blood eosinophils. A more favourable long-term slope of FEV_1 after the first three months was predicted by a larger baseline

bronchodilator response only. It was, however, impossible to predict from baseline characteristics which individual patients would not show an improvement in FEV_1 at all.

Although age, FEV_1, and bronchodilator response were all mono-variable predictors of response in PC_{20} to inhaled corticosteroids, in **chapter 10** it is shown that only total serum IgE is an *independent* predictor of response in PC_{20} to steroids. Total serum IgE proved to be a better independent predictor of changes in PC_{20} during corticosteroids than other allergy parameters including house dust mite specific IgE, skin test for house dust mite, sum of skin tests to 12 common aeroallergens, number of positive skin tests (of 12), and blood eosinophil count.

Oral corticosteroids are known to be extremely powerful agents in many chronic inflammatory diseases, amongst them obstructive airways disease. However, they provoke serious side-effects, one of them being osteoporosis, leading to fractures. Inhaled corticosteroids may be absorbed systemically, so since the introduction of *inhaled* corticosteroids more than 20 years ago, there has been a constant watch for side effects analogous to those of oral steroids. With the recent introduction of novel serum parameters of bone metabolism, especially osteocalcin, renewed concern has arisen over the effects of inhaled corticosteroids on bone turnover. In **chapter 11** the effects of inhaled corticosteroids on bone metabolism were monitored with several serum and urinary parameters over 2.5 years of treatment. No clear-cut effect on bone formation or resorption with inhaled corticosteroids was found.

Although the airways hyperresponsiveness is a relatively well established risk factor for obstructive airways disease is, the significance of asymptomatic airways hyperresponsiveness is less clear. In a separate epidemiological study, described in **chapter 12**, Borg dyspnoea scores were used to rate dyspnea before and after a histamine challenge test. It was found that many asymptomatic hyperresponders do not perceive the changes in airways obstruction as breathlessness.

Finally, our experience in setting up and conducting a long-term multi-centre trial is discussed in **chapter 13**. It is stressed that primary and secondary end points should be defined in advance. Our experience shows that it may be hard to recruit sufficient numbers of patients for a long-term trial. A feasibility study is a useful tool in implementing a standardized protocol and evaluating patient recruitment rates.
During the conduct of a long-term clinical trial, continuing quality control is of utmost importance. Frequent interim analyses should be undertaken by an independent committee on the basis of predefined end points and significance levels that are stricter than those at the normal termination of a study. Ongoing motivation of patients and staff is important to avoid trial fatigue.

14.2 Discussion

14.2.1 Limitations of the study

The patients entered in this study were selected in 6 hospitals. This implies that their disease was severe enough to visit a pulmonary physician instead of their general physician. It is also possible that a selection was introduced because of the fact that only